Result Page

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Titrate: Method of preparation of a compound of interaction of a derivative anilide with a porous support by fluid supercritical

The present invention relates to a process of interaction of a derivative of anilide nanoparticulaire with a porous support, by the technology of fluid supercritical, in particular that of COx.

The new pharmaceutical molecules with strong added value, like the derivatives of anilide, are in 40% of the cases insoluble or not very soluble in water, which night with their bioavailability. The increase of the specific surface of the powders makes it possible to improve their speed of dissolution.

Gold the bioavailability of the active principles can considerably be increased if their speed of dissolution is improved.

The generation of fine powders of specific surfaces raised by the technology of fluid supercritical is used since about fifteen year.

Two types of, proceeded are conventionally implemented: the process LMBO (Rapid Expansion off Supercritical Solution), and process SAS (Solvent-Anti-Solvent). By modification of the operating conditions, it is possible to control the morphology and the size of the formed particles of active substance.

The benefits of use of supercritical C02 as a solvent are multiple: - Possibility of working with low temperature (> 31 C3 for the therrnosensibles active substances, - To be able readily modulatable solvent while exploiting the parameters of the process (pressure, temperature, flow...), - easy Separation of the mixture solvent-aqueous solution by single decompression, - chemical Inertia of solvent: not-toxic, not-flammable, non-corrosive, - lesser Cost compared to organic solvents conventionally used.

In the fields pharmaceutical, cosmetic and nutraceutic, there is a certain number of patents and publications relative with the microencapsulation of an active substance in a coating agent. Nevertheless, the majority of the described processes do not relate to the improvement of the bioavailability, but rather the adsorption of an active substance on a support.

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Bertucco and Al (Drugs encapsulation usifag has compressed gas off antisolvent technical-Proceedings the 4th Italian Conference one Supercitical Fluids and to their Applications 1997, 327-334-ED. E. Reverchon) describe a process in which, one puts in suspension the active substance in a polymeric solution of bio playing the part of the support. This suspension, placed in the autoclave, is then bringing in the presence of supercritical CO2 for the désolvater (extraction of solvent by fluid supercritical) and to involve the complexation of the support by supersaturation on the active substance. This process is a process batch, in which the active substance is not precipitated by the fluid supercritical one since it is in suspension. The structure of the particles of active substance is thus unchanged, which does not contribute to improve its dissolution in an aqueous medium.

An identical process is described by Benoît and Al in their request for W098/13136 patent.

Another technical of deposition of a support, consists in solubilizing the aforementioned support in the fluid supercritical one, then to make precipitate this support on the active substance. For this making, the active substance and its support are previously placed in the agitated autoclave, and the supercritical injection of C02 solubilizes only the support (this implies that the support is soluble in the fluid supercritical one and that the active substance is not it), which is precipitated by modification of the pressure and the temperature within the autoclave. In this case, the initial structure of the active substance remains unchanged, and it is difficult to control the ratio active substance/support obtained in the precipitated complex. This process batch is detailed in the demand for patent EP 706.821 of Benoit and Al

The process of microencapsulation describes by Shine and Gelb in their request for W098/15348 patent consists of: 1. To mix an active substance with polymeric of encapsulation, 2. To liquify the polymeric one by passage of a flow of fluid supercritical, 3. To rapidly depressurize in order to solidify the polymeric one around the active substance.

This process is applicable only with one active substance and polymeric insoluble in the fluid supercritical one. So the active substance preserves its structure of origin, which does not contribute to improve its bioavailability.

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In the demand for patent FR2798863 of Perrut and Majewski, the active substance (kava-kava, curcuma, mixture of black pepper and mild paprika), previously extracted by fluid supercritical, is precipitated in an autoclave containing a porous support. The studied porous medium is the maltodextrin. It is thus about a single inclusion in a porous support without step of diffusion in static mode of the active substance in its support. Gold precipitation on a support is not sufficient to improve in a consequent way the solubility of the active substance in aqueous medium.

The team of Tomasko (Cabbage and Al, composite GAS crystallization off polymer-pharmaceutical particles, Proceedings off the 4 ' HT International Symposium one Supercritical Fluids, 1997,55-57 and Kim J. - H. and Al, Nicroencapsulation off Naproxen using Rapid Expansion off Supercritical Solutions, Biotechnol. Prog. 1996, 12, 650-661) mentions two processes of coprecipitation per LMBO and SAS with of supercritical C02. The studied active substance is the naproxen, while the support is the poly-L-lactic acid (L-PLA). These two made up is dissolved simultaneously in the acetone front to be precipitated by injection of C02 with counter-current, in the case of process SAS. The complex thus formed is recovered after a time of washing. A mixture of naproxen and L PLA are placed in an enclosure, from which the two made up ones are extracted by the fluid supercritical one, and are precipitated in a second autoclave, concerning process LMBO. Gold the precipitation or coprecipitation of an active substance and a support is not sufficient to improve in a consequent way the solubility of the active substance in aqueous medium. Moreover, there still, no step of molecular diffusion in static mode in order to improve the interpenetration of the active substance with its support is described in these two processes. Finally the solubility of the active substance in an aqueous medium is not studied.

It is the same for the processes of coprecipitation described by Sze You and Al (Applications off dense gases N pharmaceutical processing, Proceedings off the 5th Meeting one Supercritical Fluids 1998, Volume 1, 263-269), Weber and Al

(Coprecipitation with compressed antisolvents for the manufacture off microcofnposites, Proceedings off the 5h Meeting one Supercritical Fluids 1998, Volume 1, 243-248) and Bleich and Müller (Production off drug loaded by the uses off

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supercr-itical gases with t7ze Aerosol Solvefat Extraction System (ADZES) process, J.

Microencapsulation 1996,13, 131-139).

Subramaniam and Al in their request for W097/31691 patent developed equipment and a process starting from antisolvants near of the critical point and supercritical, which makes it possible to precipitate and coat with the particles. The phase of contact between the solution,

the suspension containing the aqueous solution, and antisolvant it supercritical is made so that it generates waves of high frequencies, which divide the solution into a multitude of small drops. In this patent, the size of the particles asserted is 0,1 to 10 um. In addition, of the processes of coating are also described. Crystallizations of hydrocortisone, of the poly (D, Lactide glycolidic), of ibuprofene and the camptothecin are described. Gold the precipitation or coprecipitation of an active substance and a support is not sufficient to improve in a consequent way the solubility of the active substance in aqueous medium. Moreover, this process does not describe a molecular step of diffusion in static mode making it possible to improve the bioavailability of the active substance.

Tom and Al (Applications off supercritical fluids in controlled release off drugs, Supercritical Fluids Engineering Science ACS Symp. Ser. 514, American Chemical Society, Washington cd., 1992) bring back the first coprecipitation by process LMBO of microparticles of active substance of lovastatine (anticholestérolémiant) complexed to polymeric, the DL-PLA. The two made up ones are placed in an autoclave, extracted by C (32 supercritical and precipitated in one second enclosure. The major disadvantage of such a process is the ratio active substance/support obtained in the complex. Indeed, this ratio cannot be selected accurately since it determined by the solubility of each of both is composed in C02 with the supercritical state. Gold the coprecipitation of an active substance and a support is not sufficient to improve in a consequent way the solubility of the active substance in aqueous medium. Moreover this process does not describe a molecular step of diffusion in static mode making it possible to improve the bioavailability of the active substance, and moreover, its solubility in an aqueous medium is not studied.

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A process of impregnation active the, pharmaceutical ones is asserted in the demand for patent WO 99/25322 of Carli and Al It breaks up in the following way: 1. Solubilization of the active principle by process LMBO, 2. Bringing in contact of fluid supercritical containing the active principle with the polymeric crosslinked one, 3. Impregnation of polymeric crosslinked in static or dynamic mode, 4. Elimination of fluid supercritical.

Single of the soluble active substances in the fluid supercritical one can be prepared by this process, since the first step consists of the extraction of the active principle by the fluid supercritical one. In addition, the process is not a process of inclusion but of impregnation on a support, and no result is given concerning the improvement of dissolution in an aqueous medium of the active principle thus prepared. Lastly, the polymeric impregnated one does not undergo a step of washing by fluid supercritical.

Fisher and Müller describe in their US patent 5.043.280 a method of preparation of active substances on a support by fluid supercritical. This process consists in putting in active contact one or more (S) with one or more support (S) of supercritical medium. For this

making the active ones and the supports either are precipitated, or Co-precipitates by processes SAS and/or LMBO. The compounds are obtained in sterile form. Gold the precipitation or coprecipitation of an active substance and a support is not sufficient to improve in a consequent way the solubility of the active substance in aqueous medium. Moreover this process does not describe a molecular step of diffusion in static mode making it possible to improve the bioavailability of the active substance, and moreover, its solubility in an aqueous medium is not studied.

Van Hees and Al (Application off supercritical carbon dioxide for the preparation off has Piroxicain-, 6-cyclodextrin inclusion conipound, Pharmaceutical Research, Vol.

16, NR 12, 1999) describe in their publication a process of inclusion of Piroxicam in (3-cyclodextrins by supercritical COa. The process consists in placing a mixture of Piroxicam and p-cyclodextrins (molar ratio 1/2,5) in a pressurized autoclave, left in static mode. After depressurisation the obtained mixture is crushed and homogenized front characterizing.

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These analyses make it possible to conclude as for the rate from complexation from Piroxicam with P-cyclodextrin, but do not give any result on the improvement of dissolution in aqueous medium of the complex Piroxicam/P-cyclodextrin compared to single Piroxicam. Moreover, the active substance used was not generated by fluid supercritical and no step of washing by fluid supercritical of the complex is carried out.

Kamihira Mr. and Al (Formation off will inclusiora coTnplexes between cyclodextritzs and aromatic compounds urader presszarized carbon. dioxide, J. off Fermentation and Bioengineering, Flight. 69, NR 6, 350-353, 1990) describe a process of extraction of aromatic compounds volatile, and trapping by inclusion in cyclodextrins. The géraniol and oils it mustard is thus extracted by a process LMBO, and is vaporized in dynamic mode in a second autoclave containing a mixture of cyclodextrin and water. The influence of the parameters temperature, pressure and water content is studied by measurement of the rate of inclusion of the active substances in cyclodextrins. The step of inclusion described in this publication is carried out in dynamic and nonstatic mode, as asserted in the present invention. In addition this process does not include/understand a step of washing by fluid supercritical. Lastly, the solubility of the active substance in an aqueous medium is not studied.

Sze You L. and Al (Application off dense gauzes in pharfnaceutical processing, Proceedings off 5th meeting one supercritical fluids, Nice, France, March 1998) describe in their publication how to practise a precipitation by SAS of an active substance (parahydrobenzoïque acid) and the polymeric ones (PLGA- polylactictide Co-glycolide-or PLA-poly L-lactic acid). This coprecipitation is carried out following two technical; maybe

with the polymeric one and active substance in two different solutions; or else in the same solution. In the two cases, two solutions, or the solution, containing the two components are treated by supercritical SAS C02. Gold, the coprecipitation of an active substance and a porous support is not sufficient to improve in a consequent way the solubility of the active substance in aqueous medium. Moreover, this method does not describe a molecular step of diffusion in static mode making it possible to improve the bioavailability of the active substance, and, moreover, its solubility in an aqueous medium is not studied.

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It is the same for the processes of coprecipitation described by Jung and Al in their patent FR 2.815.540. It is about a manufactoring process of very fine particles containing at least an active principle inserted in a molecule host, as well as a device allowing the bringing in work of this process. This process consists in putting in solution the active principle in a first liquid solvent, and a formed product of the molecules hosts, cyclodextrins type or ether-crown, in a second liquid solvent. The solutions are then bringings in contact with fluid with supercritical pressure, in order to make precipitate the molecules, according to a process SAS. The components, as in the process describes by Sze You L. in the article quoted previously, can be solubilized in same solvent. Results presented by Jung and Al do not assert improvement the speed of dissolution. Gold, the coprecipitation of an active substance and a support of the cyclodextrin type is not sufficient to improve in a consequent way the solubility of the active substance in aqueous medium. Moreover, this method does not describe a molecular step of diffusion in static mode making it possible to improve the bioavailability of the active substance, and, moreover, its solubility in an aqueous medium is not studied.

Moreover any the documents of the former art quoted above do not describe a process of inclusion of a derivative of anilide on a porous support.

In a surprising way the inventors of the present request have exposed that a process including/ understanding the steps of generation of a derivative of anilide by fluid supercritical, its mixture with a porous support followed by a molecular step of diffusion by the fluid supercritical one in static mode and of washing by the fluid supercritical one made it possible to prepare a compound of interaction by increasing very highly solubility in an aqueous medium of derived the anilide, and thus its bioavailability.

Indeed, the step of inclusion in static mode coupled with the phase of precipitation of derivative of anilide to its support allowed in a surprising way to improve dissolution of derived from anilide in aqueous medium. Moreover, the third phase of washing in supercritical medium, which consists in eliminating residual solvents by passage from a flow of supercritical C02 allows also, of

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surprising way, in addition to the washing of composed of interaction, to increase consecutive dissolution with this step.

Moreover, these steps can be carried out in batch or uninterrupted, as it is especially the case for the diffusion and washing. That thus makes it possible to reduce the process compared to the conventional steps which would be: 1. Crystallization 2. Solid/liquid separation 3. Drying 4. Inclusion in support 5. Micronization
Thus, the present invention relates to a method of preparation of a compound of interaction of a derivative of anilide with a porous support, characterized in that it includes/understands the following steps: (A) To intimately mix preferably the derivative of anilide generated by fluid supercritical and the determined quantity of porous support, (b) To implement a molecular step of diffusion per bringing in contact in static mode of fluid supercritical with the pendent obtained mixture at the step (A) time necessary to improve dissolution in an aqueous medium of the obtained mixture to the step (A), (c) To wash the compound of interaction obtained with the step (b) by a flow of fluid supercritical, (D) To recover the particles of made up of interaction thus formed.

By derived from anilide, one hears within the meaning of the present invention very derived from anilide. It is in a beneficial way of a derivative about general formula 1 following: EMI8.1

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in which: Identical or different IH and R2 represent independently one of other hydrogen atom; a radical alkyl linear or ramified out of Cl-C6; an aromatic grouping such as phenyl, naphthyl or pyridyl optionally substituted by one or more groupings alkyl in Ci-C4, Cl-C4 alcoxy, hydroxyl or halogéno, R3 represents a chain alkyl linear or ramified in C6-Cz5 or a grouping phenyl optionally substituted by one or more groupings alkyl in Ci C4, Cl-C4 alcoxy, hydroxyl or halogéno, A represents a sulphur atom or of oxygen or the grouping sulfoxy.

In a way even more beneficial, they are (S) the -2 ', 3 ', 5 ' - trimethyl-4'-hydroxy-A dodécylthiophényl acetanilide (F12511). The compounds of formula 1 being able to have centers of asymmetry, the derivative of anilide according to the present invention can be one of different the stéréoisomères or enantiomers or their mixture. These derivatives and their mode of preparation are described in the demand for patent FR 2.741.619.

By derived from anilide generated by fluid supercritical, one hears within the meaning of the present invention, any derivative of anilide such as defined above which has undergoes a step of generation by fluid supercritical, i.e. a step allowing thanks to the use of fluid

supercritical to increase his specific surface.

Preferably E such step consists of a process LMBO or SAS.

By porous support. one hears within the meaning of the present invention any soluble suitable porous support in an aqueous medium. Preferably the porous support is selected in the group consisted cyclodextrins and their mixture. In a beneficial way, it is about there-cyclodextrin.

By fluid supercritical, one hears within the meaning of the present very fluid invention used at a temperature and a great pressure with their critical value.

Preferably it is about CO2.

By Static mode one hears within the meaning of the present invention a reaction or a process in which all the reactive ones are put simultaneously in presence and where one lets the reaction be held. For example, in the step (b) of the present invention, one puts in an autoclave a Co-crystallized powder, water and of C02

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supercritical and one lets react pendent 16 Hours. The mass of product does not evolve/move during the reaction.

Contrary, in dynamic mode, the reactive ones are progressively brought evolution of the reaction or production. Often in the frame of a dynamic mode, there are circulation of fluid or agitation. The mass of product evolves/moves during the production. In the process of the present invention, the step (A) is typically a dynamic phase.

By intimate mixture, one hears within the meaning of the present invention a mixture of A and B in which A and B are found uniformly distributed within the obtained mixture.

In an embodiment particular, the process according to the present invention is such as the porous support is generated by fluid supercritical and that the step (A) includes/understands the following steps: (Al) To put in solution the derivative of anilide and the support porous in an organic solvent, the aforementioned organic solvent being soluble in the fluid supercritical one, (a2) continuously To put in contact the solution obtained at step (Al) with the aforementioned fluid supercritical, in order to désolvater in a controlled way the derivative of anilide and the support, and to ensure their coacervation, (a3) To wash the complex thus formed by extraction of residual solvent by the fluid supercritical one, then to carry out the separation of solvent to the liquid state and fluid supercritical with the gaseous state.

Preferably the step (A) consists of a coprecipitation, derivative of anilide and support porous by process SAS.

In another embodiment, the process according to the present invention is such as the derivative of anilide, front its use in the step (A), is generated by the process including/ understanding the following steps: (I) To put in solution the derivative of anilide in an organic solvent, the aforementioned organic solvent being soluble in the fluid supercritical one,

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(II) Continuously to put in contact the solution obtained at the step (I) with the aforementioned fluid supercritical, in order to désolvater the derivative of anilide, and to ensure its coacervation, (III) Laver particles of derived from anilide thus formed by extraction of residual solvent by the aforementioned fluid supercritical, then to carry out the separation of solvent to the liquid state and fluid supercritical with the gaseous state, and that the porous support used with the step (A) is in solid form.

Preferably the derivative of anilide, front its use in the step (A), is generated by precipitation according to process SAS.

In a third embodiment, the process according to the present invention is such as the derivative of anilide, front its use in the step (A) is generated by the process including/ understanding the following steps: (I) To extract the derivative from anilide by the fluid supercritical one, optionally added with a Co-solvent, (II) Vaporiser the supercritical mixture in order to désolvater the derivative of anilide, and to ensure its coacervation, (III) Laver particles of derived from anilide thus formed by the fluid supercritical one, then optionally to carry out the separation of Co-solvent to the liquid state and fluid supercritical with the gaseous state, and that the porous support used with the step (A) is in solid form.

Preferably, the derivative of anilide, front its use in the step (A), is generated by precipitation according to process LMBO.

In a fourth embodiment, the process according to the present invention is such as the step (A) includes/understands the following steps: (Al) To put in solution the derivative of anilide in an organic solvent, the aforementioned organic solvent being soluble in the fluid supercritical one, (a2) continuously To put in contact the solution thus obtained with the fluid supercritical one, in order to désolvater the derivative of anilide, and to ensure its coacervation on the porous support previously placed in the engine,

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(a3) To wash the complex thus formed by extraction of residual solvent by the fluid supercritical one, then to carry out the separation of solvent to the liquid state and fluid supercritical with the gaseous state.

Preferably, the step (A) consists of precipitation by process SAS of derived from anilide on the porous support.

In a fifth embodiment, the process according to the present invention is such as the step (A) includes/understands the following steps: (Al) To extract the derivative from anilide by fluid supercritical, optionally added with a Co-solvent, (a2) To vaporize the supercritical mixture in order to désolvater the derivative of anilide, and to ensure its coacervation on the porous support previously placed in the engine, (a3) To wash the complex thus formed by the fluid supercritical one, then optionally to carry out the separation of Co-solvent to the liquid state and fluid supercritical with the gaseous state.

Preferably, the step (A) consists of precipitation by process LMBO of derived from anilide on the porous support.

In a beneficial way, the organic solvent or the Co-solvent east chooses in the group consisted alcohols, in particular methanol or butanol, ketones, in particular acetone, the methylethylketone, cyclohexanone or N methylpyrrolidone, the acetic acid, ethyl acetate, dichloromethane, acetonitrile, the diméthylformamide, diméthylsulfoxyde (DMSO) and their mixture. Preferably it is of ethanol or diméthylsulfoxyde.

In a beneficial way, the step (molecular b) of diffusion of the process according to the present invention is carried out under agitation.

In a way even more beneficial, the step (molecular b) of diffusion of the process according to the present invention is carried out in the presence of an agent of diffusion.

By agent of diffusion, one hears within the meaning of the present invention any solvent supporting an interaction of derived from anilide with the support.

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Preferably, this agent of diffusion is selected in the group consisted alcohol, water with or without surfactant agent and their mixtures. In a way even more beneficial, it is about water.

This agent of diffusion can be added uninterrupted or into discontinuous.

Time necessary with the molecular diffusion of the step (b) is determined by any suitable

method. This step (b) can as many be reiterated time as desired to obtain a speed of satisfying dissolution. Preferably, the step (b) hard approximately 16 hours.

The conditions of pressure and temperature of the step (b) are selected in order to support the molecular diffusion. Preferably the pressure of fluid supercritical lies between 10 MPa and 40 MPa and the temperature between 0 and 120 C.

In a way even more beneficial, the fluid supercritical one is used with a pressure ranging between 10 MPa and 40 MPa and at a temperature ranging between 0 and 120 C in all the steps of the process according to the present invention.

Preferably each step of the process according to the present invention is bringing works about it in a closed engine, in particular an autoclave.

In a beneficial way the process according to the present invention is carried out uninterrupted.

The present invention also relates to a compound of interaction of derived from anilide with a porous support characterized in that it is capable to be obtained by the process according to the present invention.

In a beneficial way, the compound of interaction according to the present invention is such as the derivative of anilide thus complexed present a solubility in an aqueous solution of sodium Laurylsulfate with 5% great with approximately 600 tg/ml.

The present invention concerns moreover one made up of interaction according to the present invention as a medicament, preferably intended to treat dyslipidémies such as the hypercholesterolemy and/or with the prevention of the arteriosclerosis.

It also relates to the use of a compound of interaction according to the present invention for the manufacture of a medicament intended for the treatment of

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dyslipidémies such as the hypercholesterolemy and/or with the prevention of the arteriosclerosis.

Physical characteristics of the powders to the different steps: Powders active principle obtained by LMBO: - extremely slight and pulverulent powder, - size and type of monodispersed crystals: sticks length of 1-3, um and of diameter 100 to 200 Nm, - apparent density of 12 kg/m3.

Powders active principle obtained by SAS: - Very slight and pulverulent Powder, - size and type of monodispersed crystals: sticks 10-20 m length and diameter 100 Nm, - apparent density 97 kg/m3.

Co-crystallized powder (principle actifcyclodextrine) - slight and pulverulent fine powder, apparent density 176 kg/m3 Co-crystallized Powder, maturée (active principle/cyclodextrin) - dense and nonpulverulent powder, - apparent density 639 kg/m3.

Other objects and benefits of the invention will become apparent for the specialist of the profession starting from description detailed below and by the means of references to the following illustrative drawings.

The figure L represents a photo MEB with an enlarging of 1000x of the F12511 product obtained after crystallization and drying by conventional way.

Figure 2 represents a photo MEB with an enlarging of 2000x of the F12511 product obtained after crystallization and drying by conventional way.

Figure 3 represents a photo MEB with an enlarging of 1.000x of the complex obtained after coprecipitation by process SAS and washing by supercritical CO2 of a solution of the F12511 product and of there-cyclodextrin in the DMSO.

Figure 4 represents a photo MEB with an enlarging of 2000x of the complex obtained after coprecipitation by process SAS and washing by C02

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supercritical of a solution of the F12511 product and there-cyclodextrin in the DMSO.

Figure 5 represents a photo MEB with an enlarging of 1000x of the same complex as figures 3 and 4 after 16 hours of molecular diffusion in supercritical medium, in the presence of water.

Figure 6 represents a photo MEB with an enlarging of 2000x of the same complex as figures 3 and 4 after 16 hours of molecular diffusion in supercritical medium, in the presence of water.

Figure 7 represents a histogram of the bioavailability of the F12511 product according to the formulation used (compound of interaction with the-cyclodextrin according to the process of the present invention or produced crystallized F12511) in the dog.

The process according to the invention includes/understands especially a molecular step of diffusion in supercritical medium allowing a strong interaction of the particles of derived from anilide in the support considered, as the photographs achieved by means of an electronic scanning microscope show it (figures 1 to 6). One can see on these photographs which the structure of the compound is completely modified during the diffusion.

Moreover, dissolution in aqueous medium is also modified.

Thus, the compound according to figures' 1 and 2 A a solubility at the end of 2 hours of 6 ug/ml in an aqueous solution with 5% of lauryl sulphates sodium.

The complex according to figures' 3 and 4 A a solubility at the end of 2 hours of 86 llg/ml in an aqueous solution with 5% of lauryl sulphates sodium.

The complex according to figures' 5 and 6 A a solubility at the end of 2 hours of 516 ug/ml in an aqueous solution with 5% of lauryl sulphates sodium.

The desired objective during this step of diffusion is to improve dissolution of the microparticles of active substance.

The following step which is a step of washing by fluid supercritical, still makes it possible to increase the speed of dissolution of composed of interaction of derived from anilide in the porous support.

Dissolution at the end of two hours in an aqueous medium is multiplied by approximately 100 by the process according to the present invention.

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The examples following of bringing in work of the process are given nonrestrictive as an indication.

Protocols of analysis of the powders Tests of dissolution of the product F12511 Operating conditions: Controlled spectrophotometric detector with 220 Nm.

Column grafting C8 (Lichrospher 60RP-Select B), dimensions 25 X 0,4 cm, granulometry: 5 Mr.

Mobile phase: * Acetonitrile 820 ml * purified Water 180 ml * Glacial acetic acid 1 ml Flow: 1 ml/min Preparation of the solutions: Solution to examine Introduire a quantity of corresponding complex to approximately 100 Mg of the F12511 product into 100 ml of lauryl sulphates sodium with 5% (m/V) in H2O. To place under magnetic agitation in a bain-

marie at 37 C 0, 5 C. To take 2 ml of this suspension after 2 hours of agitation and to filter on filter GELMAN GHP ACRODISC GF (R).

To dilute the taking away to the 1/5 in the mobile phase.

To carry out 2 tests.

Pilot solution To introduce 8 Mg of the F12511 product of reference (raw material having been used for manufacture of the complex) into a flask of 100 ml, to dissolve in 1 ml of tétrahydrofurane (THF).

To supplement with volume with the mobile phase.

Range
EMI16.1

<Tb>
<Tb> <SEP> T1 <SEP> T2 <SEP> T3 <SEP> T4 <SEP> T5
<Tb>
<Tb>
<Tb> Solution <SEP> witness <SEP> (ml) <SEP> 0,5 <SEP> 1,5 <SEP> 2,0 <SEP> 3,0 <SEP> 4,0
<Tb>
<Tb>
<Tb> Phase <SEP> mobile <SEP> qsp <SEP> 20 <SEP> ml
<Tb>
<Tb> Concentration <SEP> (tg/nil) <SEP> 2, <SEP> 0 <SEP> 6,0 <SEP> 8,0 <SEP> 12,0 <SEP> 16,0
<Tb>

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Realization of the test: To inject 20 U. L of each pilot solution. To measure the surface of the peak of the F12511 product and to graphically represent its variation according to the concentration. The coefficient of correlation is > 0,995. To inject 20 ul solution test. To measure the surface of the peak of present the F12511 product in the solution test, and to make sure that it lies between that of the T1 and T5 of the range.

In the opposite case, to carry out a dilution in solvent of solubilization and/or to adjust the volume of injection of the solution test.

In deducing concentration X (, ug/ml) from the solution test.

To calculate the quantity of the F12511 product solubilized in mg/ml by the formula: Xx20xFx5
1000 X THERE Y: volume of injection of the solution test F: spécif factor of Mesures dilution of surfaces ques the measurements of specific surface was carried out on an apparatus with adsorption Study Bureau ASAP 2010, Micrometrics.

Preparation of the sample Front the phase of measurement, the sample requires a step of degasification. This step consists in making the empty one in the cell containing the sample until one reached at least empty of 0, 003 mm Hg, are approximately 0,004 mbar, and this of stable manner. This degasification is carried out at a temperature of 50 C (lasted: approximately 16 hours).

Into fine of degasification, the cell containing the sample is filled with helium, and transferred to the station from measurement where one remakes the empty front analyzes.

Exploitation of isothermal of adsorption the determination of specific surface was made according to theory Study Bureau, that is to say according to the relation: 1 1 + C-1. (P/Po) W. [(Po/P) - 1] CWmWm. C

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W: volume of adsorbed gas (under the conditions standard of temperature and pressure (STP)) by unit of mass of sample.

Wm: volume of gas adsorbed (under conditions STP) in a monolayer per unit of mass of sample.

Po: saturated vapour pressure.

C: constant.

One then recalls the isothermal one according to:
1
W. [(Po/P) - 1] According to P/Po: we have straight then whose slope and ordinate with the origin give us C and Wm.

Specific surface is then given by the formula: has (my. g-13=NmNAE E: obstruction of the nitrogen molecule. One takes generally for nitrogen to 77 K, operational temperature, E = 0, 162 nm2.

NA: number of Avogadro.

Nm: number of mole of nitrogen adsorbed on a monolayer per unit of mass of sample, calculated starting from Wm.

The measurements are carried out in a conventional field of relative pressure where theory Study Bureau is valid, that is to say 10, 05 < P/Po < 0, 2. To check the validity of this theory, a practical mean is to look in which direction evolves/moves the Nadsorbé quantity. (1-P/Po) according to P/Po: it must continuously increase with P/Po.

To check this manner the field of applicability of theory Study Bureau, and to readjust if need be, the field of the relative pressures.

Comparative example 1: precipitation by SAS/DMSO of the F12511 product a solution of 150 ml of concentration: 115 g/1 of the F12511 product in the DMSO, is precipitated uninterrupted by the process Solvent-Anti-Solvent (SAS) in the presence of CO2, in an autoclave of 21 provided with a basket of 1,371. The flow of the pump solvent is of 0,6 ml/ min. The temperature and the pressure within the autoclave are selected to obtain an equal density of CO2 with 0,8. After to have

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precipitate approximately 130 ml of solution, the injections of the aqueous solution then of C02 are stopped, and one carries out washing by passage of a CO2 flow (300 bars, 50 c) pendent 3 hours. The autoclave is then depressurized. The output of this step is 87%.
EMI19.1

<Tb> <SEP> Nature <SEP> <SEP> <the SEP> SEP <powders> Dissolution <SEP> (lg/ml) <SEP> STUDY BUREAU <SEP> (m/g)
<Tb>
<Tb> <SEP> F <SEP> 12511 <SEP> 6-12 <SEP> 14
<Tb>
<Tb> F <SEP> 12511 <SEP> precipitate <SEP> by <SEP> SAS <SEP> 62 <SEP> 54
<Tb>
Comparative example 2: precipitation by LMBO of the product F12511 One places 10 G of F12511 product in an autoclave, which one extracts by from supercritical C02 at 100 C, 265 bars. The fluid one is then precipitated in a second enclosure, and one recovers 0, 6 G of F12511 product. One measurement dissolution at the end of two hours as well as specific surface:
EMI19.2

<Tb>
<Tb> Nature <SEP> <SEP> <the SEP> SEP <powders> Dissolution <SEP> (ug/ml) <SEP> STUDY BUREAU <SEP> (m/g)

<Tb> F <SEP> 125111214
<Tb>
<Tb> F <SEP> 12511 <SEP> precipitate <SEP> by <SEP> LMBO <SEP> 76 <SEP> 67
<Tb>
Comparative example 3: lco-precinitation of the F12511 product and the ycyclodextrine by SAS/DMSO a solution of 150 ml of product F12511 (concentration: 57,5 g/1) and of ycyclodextrine (concentration of 172,5 g/1) in the DMSO, is precipitated uninterrupted by the process Solvent-Anti-Solvent (SAS) in the presence of CO2, in an autoclave of 21 provided with a basket of 1,371. The flow of the pump solvent is of 0,4 mUmin. The temperature and the pressure within the autoclave are selected to obtain an equal density of C02 with 0,9. After to have precipitated approximately 100 ml of solution, the injections of the aqueous solution then of C02 are stopped, and one carries out the washing of the powder obtained by passage of a flow of C02 (300 bars, 50 C) pendent 2 hours.

The autoclave is then depressurized.

The output of this step is 81%.

<Desc/Clms Page number 20>

The results of the measurements of dissolution are gathered in the table below:
EMI20.1

<Tb> Nature <SEP> <SEP> <the SEP> SEP <powders> 9 <SEP> Dissolution <SEP> (, <SEP> ig/mlj
<Tb>
<Tb> F <SEP> 12511 <SEP> 12
<Tb>
<Tb> F <SEP> 12511 <SEP> Co-précipitépar <SEP> SAS/D1VISO <SEP> 100
<Tb>
Example 4: coprecipitation inclusion and washing with, to start from a solution of the F12511 product and γ-cyclodextrin in the DMSO
A solution of 450 ml of the product F12511 (concentration: 40 g/1) and of y cyclodextrin (concentration of 240 g/1) in the DMSO, is precipitated uninterrupted by the process Solvent-Anti-Solvent (SAS) in the presence of C02, in an autoclave of 61 provided with a basket of 41. The flow of the pump solvent is of 1,1 ml/min. The temperature and the pressure within the autoclave are selected to obtain an equal density of COa with 0,9 ~ 0,05. After to have precipitated approximately 450 ml of solution, the injections of the aqueous solution then of C02 are stopped, and one proceeds to the mild relaxation of the installation, in order not to liquify the fluid supercritical one.

The output mean of this step is 94%.

One mixture the powder Co-precipitated with the preceding step with osmosée water (mass ratio of water 25%), and the mixture is placed in the basket poral of 4L, itself deposited in the autoclave of precipitation of 6 1.

The autoclave is closed, and one inflates the installation in supercritical C02 in order to have a static pressure of 300 bars, and a temperature of 65 C within the autoclave.

One proceeds to the mild relaxation after a molecular night of diffusion, and one reiterates this step, without addition of agent of diffusion (water) pendent one night.

Then one carries out the washing of the complex thus obtained by flow of supercritical COa (270 bars, 40 C) pendent 8 hours. One after carries out relaxation a measurement of dissolution on the powder obtained.

<Desc/Clms Page number 21>

EMI21.1

<Tb>

<SEP> Nature <SEP> <SEP> <the SEP> SEP <powders> Dissolution <SEP> (llg/ml)
<Tb>
<Tb> <SEP> F12511 <SEP> front <SEP> coprecipitation <SEP> 115
<Tb>
<Tb> <SEP> Composed <SEP> F12511/y-cyclodextrin <SEP> after <SEP> 440
<Tb>
<Tb> <SEP> diffusion <SEP> molecular
<Tb>
<Tb> Composed <SEP> F12511/y-cyclodextrin <SEP> after <SEP> 662
<Tb>
<Tb> <SEP> diffusion <SEP> molecular <SEP> and <SEP> washed
<Tb>

These results show the interest of a process associating the coprecipitation, the interaction and washing in supercritical medium to improve dissolution in aqueous medium of derived from anilide.

Pharmacokinetic tests on the dog were carried out with a compound of interaction F1251 L 'there-cyclodextrin obtained by this process. Standardized amounts of 3 mg/kg were managed with 5 dogs, and the plasmatic concentration (expressed in ng/ml. h) in F12511 was measured. The results concerning F12511 obtained after crystallization and drying by

conventional way and those concerning the compound of interaction F12511//y-cyclodextrin obtained by the process describes above according to the present invention are represented in the histogram of figure 7.

It is noted that the administration of prepared amounts. from composed of interaction F12511Ay-cyclodextrin obtained by the process according to the present invention allows to improve the bioavailability in the dog of a factor 10.

Comparative example 5: precipitation and inclusion in the there-cyclodextrin of the F12511 product generated by SAS/Ethanol process
A solution of 8 1 of the product F12511 (concentration: 5 g/1) in ethanol, is precipitated uninterrupted by the process Solvent-Anti-Solvent (SAS) in the presence of CO2, in an autoclave of 61 provided with a basket of 41. The flow of the pump solvent is of 41,7 ml/ min. The temperature and the pressure within the autoclave are selected to obtain an equal density of C02 with 0,8. After to have precipitated approximately 81 of solution, the injections of the aqueous solution then of COx are stopped, and one proceeds to the mild relaxation of the installation, in order not to liquify the fluid supercritical one.

<Desc/Clms Page number 22>

One mixture 4,3 G of derived from anilide precipitated with the preceding step with 25,8 G of there-cyclodextrin and 10 G of osmosée water, and the mixture is placed in the basket poral of 41, itself deposited in the autoclave of precipitation of 61.

The autoclave is closed, and one inflates the installation out of supercritical CO2 in order to have a static pressure of 300 bars, and a temperature of 65 C within the autoclave.

One proceeds to the mild relaxation after 16 hours of molecular diffusion.
EMI22.1

<Tb>

<SEP> Nature <SEP> <SEP> <the SEP> SEP <powders> Dissolution <SEP> (in <SEP> ug/ ml) '
<Tb>
<Tb> <SEP> F <SEP> 12511 <SEP> front <SEP> precipitation <SEP> 15
<Tb>
<Tb> <SEP> F12511 <SEP> precipitate <SEP> by <SEP> C02 <SEP> supercritical <SEP> 80
<Tb>
<Tb> <SEP> Composed <SEP> F12511/y-cyclodextrin <SEP> after <SEP> 155
<Tb>

<Tb> diffusion <SEP> molecular
<Tb>
Comparative example 6: precipitation and inclusion in the there-cyclodextrin of the F12511 product venerated by process SAS/DMSO
A solution of 150 ml of the product F12511 (concentration: 200 g/1) in the DMSO, is precipitated uninterrupted by the process Solvent-Anti-Solvent (SAS) in the presence of COx, in an autoclave of 21 provided with a basket of 1,371. The flow of the pump solvent is of 0,5 ml/min. The temperature and the pressure within the autoclave are selected to obtain an equal density of C02 with 0,9. After to have precipitated approximately 135 ml of solution, the injections of the aqueous solution then of COa are stopped, and one proceeds to the mild relaxation of the installation, in order not to liquify the fluid supercritical one.

One mixture 1 G of derived from anilide precipitated with the preceding step with 6 G of there-cyclodextrin and 2,33 G of osmosée water, and the mixture is placed in the basket poral of 1,371, itself deposited in the autoclave of precipitation of 21.

The autoclave is closed, and one inflates the installation out of supercritical CO2 in order to have a static pressure of 300 bars, and a temperature of 100 C within the autoclave.

One proceeds to the mild relaxation after 16 hours of molecular diffusion.

<Desc/Clms Page number 23>

EMI23.1

<Tb>

Nature <SEP> <SEP> <the SEP> SEP <powders> Dissolution <SEP> (in <SEP> llg/ml)
<Tb>
<Tb> F <SEP> 12511 <SEP> front-precipitation <SEP> 5
<Tb>
<Tb> F12511 <SEP> precipitate <SEP> by <SEP> C02 <SEP> supercritical <SEP> 57
<Tb>
<Tb> Composed <SEP> F12511/y-cyclodextrin <SEP> after <SEP> 165
<Tb>
<Tb> diffusion <SEP> molecular
<Tb>
Comparative example 7: Inclusion in the there-cyclodextrin of the F12511 product generated by process LMBO One places 40 G of the F12511 product in a basket of 41, itself deposited in an autoclave of 61. The active substance is extracted by a supercritical mixture from C02 and of ethanol (mass 5%) and the substance is precipitated to 120 bar and 55 C.

After 3 hours, the injections of C02 and ethanol are stopped.

One mixture 8,96 G of derived from anilide precipitated with the preceding step with 53,76 G of there-cyclodextrin and 20,87 G of osmosée water, and the mixture is placed in the basket poral of 41, itself deposited in the autoclave of precipitation of 61.

The autoclave is closed, and one inflates the installation out of supercritical CO2 in order to have a static pressure of 300 bars, and a temperature of 65 C within the autoclave.

One proceeds to the mild relaxation after 16 hours of molecular diffusion.
EMI23.2

<Tb>

Nature <SEP> <SEP> <the SEP> SEP <powders> Dissolution <SEP> (in <SEP> pg/ml)
<Tb>
<Tb> F12511 <SEP> front <SEP> precipitation <SEP> 10
<Tb>
<Tb> F12511 <SEP> precipitate <SEP> by <SEP> C02 <SEP> supercritical <SEP> 8
<Tb>
<Tb> Composed <SEP> F12511/y-cyclodextrin <SEP> after <SEP> 292
<Tb>
<Tb> diffusion <SEP> molecular
<Tb>
Summarized results the table below summarizes the different processes implemented, as well as the corresponding results of dissolution, and makes it possible to deduce from it the process most adapt with manufacture from the F12511 product of dissolution raised in aqueous medium:

<Desc/Clms Page number 24>

EMI24.1

<Tb>
<Tb>
<Tb> <SEP> Process <SEP> Comp. <SEP> Comp. <SEP> Comp. <SEP> E.g. <SEP> 4 <SEP> E.g. <SEP> 4 <SEP> Comp. <SEP> Comp.
<Tb>
<Tb>
<Tb>
<Tb>
<Tb>

<SEP> E.g. <SEP> 1 <SEP> E.g. <SEP> 2 <SEP> E.g. <SEP> 3 <SEP> E.g. <SEP> 5 <SEP> Ex.5
<Tb>
<Tb>
<Tb>
<Tb>
<Tb>
<Tb> <SEP> Précipitation* <SEP> by <SEP> LMBO <SEP> X
<Tb>
<Tb>
<Tb>
<Tb>
<Tb>
<Tb>
<Tb> <SEP> Précipitation* <SEP> by <SEP> X
<Tb>
<Tb>
<Tb>
<Tb>
<Tb> <SEP> SAS/DMSO
<Tb>
<Tb>
<Tb>
<Tb>
<Tb>
<Tb> <SEP> Coprecipitation ** <SEP> XXX
<Tb>
<Tb>
<Tb>
<Tb>
<Tb>
<Tb> <SEP> by <SEP> SAS/DMSO
<Tb>
<Tb>
<Tb>
<Tb>
<Tb>
<Tb> <SEP> Précipitation* <SEP> by <SEP> X <SEP> X
<Tb>
<Tb>
<Tb>
<Tb>

<Tb>
<Tb> <SEP> SAS/EtOH
<Tb>
<Tb>
<Tb>
<Tb>
<Tb>
<Tb> <SEP> Crystallization <SEP> conventional
<Tb>
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<Tb>
<Tb>
<Tb>
<Tb> <SEP> Diffusion <SEP> molecular
<Tb>
<Tb>
<Tb>
<Tb>
<Tb>
<Tb> <SEP> agitated
<Tb>
<Tb>
<Tb>
<Tb>
<Tb>
<Tb> <SEP> Diffusion <SEP> molecular <SEP> X <SEP> X <SEP> X
<Tb>
<Tb>
<Tb>
<Tb>
<Tb>
<Tb> <SEP> not-agitated
<Tb>
<Tb>
<Tb>
<Tb>
<Tb>
<Tb> Washing <SEP> X <SEP> X <SEP> X
<Tb>
<Tb>
<Tb>
<Tb>
<Tb>

<Tb> <SEP> Dissolution <SEP> (g/ml) <SEP> 62 <SEP> 76 <SEP> 100 <SEP> 440 <SEP> 662 <SEP> 80 <SEP> 155
<Tb>

EMI24.2

<Tb>
<Tb> Process <SEP> Comp. <SEP> Comp. <SEP> Comp. <SEP> Comp. <SEP> EX.8 <SEP> E.G. <SEP> 8
<Tb> <SEP> E.g. <SEP> 6 <SEP> E.g. <SEP> 6 <SEP> E.g. <SEP> 7 <SEP> Ex.7
<Tb>
<Tb> Précipitation* <SEP> by <SEP> LMBO <SEP> X <SEP> X
<Tb>
<Tb> Précipitation* <SEP> by <SEP> X <SEP> X
<Tb>
<Tb> SAS/DMSO
<Tb>
<Tb> Coprecipitation ** <SEP> by
<Tb>
<Tb> SAS/DMSO
<Tb>
<Tb> Précipitation* <SEP> by
<Tb>
<Tb> SAS/EtOH
<Tb>
<Tb> Crystallization <SEP> conventional <SEP> X <SEP> X
<Tb>
<Tb> Diffusion <SEP> molecular <SEP> agitated <SEP> X
<Tb>
<Tb> Diffusion <SEP> molecular <SEP> non-X <SEP> XX
<Tb>
<Tb> agitated
<Tb>
<Tb> Washing <SEP> X
<Tb>
<Tb> Dissolution <SEP> (g/ml) <SEP> 57 <SEP> 165 <SEP> 8 <SEP> 292 <SEP> 124 <SEP> 334
<Tb>
* Precipitation of the single product r12511 ** Coprecipitation of a solution of the F12511 product and there-cyclodextrin

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Within sight of these results, it is clear that the process which makes it possible to obtain the most substantial dissolution of the F12511 product in an aqueous medium is the process combining the steps of generation of the F12511 product by fluid supercritical, preferably by coprecipitation of the F12511 product and there-cyclodextrin, molecular diffusion in static mode, preferably under agitation, washing.

Comparison tests 9: In order to validate the fact that it is else the complete process which enables us to obtain the final results and not one of the intermediate steps, we carried out tests of dissolution as described previously on different mixtures and we obtained following results:
EMI25.1

<Tb> <SEP> Front <SEP> diffusion <SEP> After <SEP> diffusion
<Tb>
<Tb> F12511/yCyclodextrmes <SEP> 19ug/ml <SEP> 142ag/ml
<Tb>
<Tb> Powders <SEP> crude
<Tb>
<Tb> Mixture <SEP> physical
<Tb>
<Tb> F12511/yCyclodextrmes <SEP> 69ug/ml <SEP> 150ug/ml
<Tb>
<Tb>
<Tb> Powders <SEP> crystallized <SEP> by
<Tb> SAS <SEP> separately
<Tb>
<Tb> Mixture <SEP> physical
<Tb>
<Tb> F12511/yCyclodextrines <SEP> 100 <SEP> g/ml <SEP> 671 <SEP> g/ml
<Tb>
<Tb> Powders <SEP> Co-crystallized
<Tb>

Result Page

CLAIMS 1. Proceeded of preparation of composed of interaction of derived from anilide with a porous support, characterized in that it includes/understands the following steps: (A) To mix the derivative of anilide generated by fluid supercritical and the determined quantity of porous support, (b) To implement a molecular step of diffusion per bringing in contact in static mode of fluid supercritical with the pendent obtained mixture at the step (A) time necessary to improve dissolution in an aqueous medium of the obtained mixture to the step (A), (c) To wash the compound of interaction obtained with the step (b) by a flow of fluid supercritical, (c) To recover the particles of made up of interaction thus formed.

2. Proceeded according to claim 1, characterized in that the porous support is generated by fluid supercritical and in what the step (A) includes/understands the following steps: (Al) To put in solution the derivative of anilide and the support porous in an organic solvent, the aforementioned organic solvent being soluble in the fluid supercritical one, (a2) continuously To put in contact the solution obtained at step (Al) with the aforementioned fluid supercritical, in order to désolvater in a controlled way the derivative of anilide and the support, and to ensure their coacervation, (a3) To wash the complex thus formed by extraction of residual solvent by the fluid supercritical one, then to carry out the separation of solvent to the liquid state and fluid supercritical with the gaseous state.

3. Proceeded according to claim 1, characterized in that the derivative of anilide, front its use in the step (A) is generated by the process including/understanding the following steps: (I) To put in solution the derivative of anilide in an organic solvent, the aforementioned organic solvent being soluble in the fluid supercritical one,

<Desc/Clms Page number 27>

(II) Continuously to put in contact the solution obtained at the step (I) with the aforementioned fluid supercritical, in order to désolvater the derivative of anilide, and to ensure its coacervation, (III) Laver particles of derived from anilide thus formed by extraction of residual solvent by the aforementioned fluid supercritical, then to carry out the separation of solvent to the liquid state and fluid supercritical with the gaseous state, and that

the porous support used with the step (A) is in solid form.

4. Proceeded according to claim 1, characterized in that the derivative of anilide, front its use in the step (A) is generated by the process including/understanding the following steps: (I) To extract the derivative from anilide by the fluid supercritical one, optionally added with a Co-solvent, (II) To vaporize the supercritical mixture in order to désolvater the derivative of anilide, and to ensure its coacervation, (III) To wash the particles of derived from anilide thus formed by the fluid supercritical one, then optionally to carry out separation of Co-solvent to the liquid state and fluid supercritical with the gaseous state, and in what the porous support used with the step (A) is in solid form.

5. Proceeded according to claim 1, characterized in that the step (A) includes/understands the following steps: (Al) To put in solution the derivative of anilide in an organic solvent, the aforementioned organic solvent being soluble in the fluid supercritical one, (a2) To put in contact the solution continuously. thus obtained with the fluid supercritical one, in order to désolvater the derivative of anilide, and to ensure its coacervation on the porous support previously placed in the engine, (a3) To wash the complex thus formed by extraction of residual solvent by the fluid supercritical one, then to carry out the separation of solvent to the liquid state and fluid supercritical with the gaseous state.

6. Proceeded according to claim 1, characterized in that the step (A) includes/understands the following steps:

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(Al) To extract the derivative from anilide by fluid supercritical, optionally added with a Co-solvent, (a2) To vaporize the supercritical mixture in order to désolvater the derivative of anilide, and to ensure its coacervation on the porous support previously placed in the engine, (a3) To wash the complex thus formed by the fluid supercritical one, then optionally to carry out the separation of Co-solvent to the liquid state and fluid supercritical with the gaseous state.

7. Process according to any of claims 2. to 6, characterized in that the organic solvent or the Co-solvent east chooses in the group consisted alcohols, the ketones, the acetic acid, the ethyl acetate, it. dichloromethane, the acétoni. trile, the diméthylformamide, the diméthylsulfoxide and their mixture.

8. Proceeded according to any of the preceding claims, characterized in that the fluid supercritical one is of C02.

9. Proceeded according to any of the preceding claims, characterized in that the derivative of anilide is it (S) -2 ', 3 ', 5 ' - trimethyl-4'-hydroxy-A dodécylthiophénylacétanilide.

10. Proceeded according to any of the preceding claims, characterized in that the porous support is selected in the group consisted cyclodextrins and their mixture.

11. Proceeded according to any of the preceding claims, characterized in that the step (molecular b) of diffusion is carried out under agitation.

12. Proceeded according to any of the preceding claims, characterized in that the step (molecular b) of diffusion is carried out in the presence of an agent of diffusion.

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13. Proceeded according to claim 12, characterized in that the agent of diffusion is selected in the group consisted alcohol, water with or without surfactant agent and their mixtures.

14. Proceeded according to any of the preceding claims, characterized in that the pressure of fluid supercritical lies between 10 Mpa and 40 Mpa and the temperature between 0 and 120 C.

15. Proceeded according to any of the preceding claims, characterized in that each step of the process is bringing in work in a closed engine, in particular an autoclave.

16. Proceeded according to any of the preceding claims, characterized in that it is carried out uninterrupted.

17. Composed of interaction of a derivative of anilide in a porous support characterized in that it is capable to be obtained by the process according to any of claims 1 to 16.

18. Composed according to claim 17 characterized in that the derivative of anilide thus complexed present a solubility in an aqueous solution of sodium Laurylsulfate with 5% great with approximately 600 ug/ml.

19. Composed according to any of claims 17 or 18 as a medicament.

20. Composed according to claim 19 as a medicament intended to treat dyslipidémies such as the hypercholesterolemy and/or the prevention of the arteriosclerosis.

21. Use of a compound according to any of claims 17 or 18 for the manufacture of a medicament intended for the treatment of the dyslipidémies such as the hypercholesterolemy and/or the prevention of the arteriosclerosis.